REMARKS

Claims

Claims 48–56, 58–65, 67–69 and 86–96 are currently under examination with claims 1–47, 57, 66, and 70–85 previously withdrawn from consideration due to restriction/election.

Claim amendments

The claims have been amended to correct for typographical errors and to use language in accordance with conventional US practice.

It is courteously submitted that the claim amendments do not raise new matter.

Rejection under 35 U.S.C. §112, first paragraph (biological deposit)

The rejection of claims 62 and 63 under §112, ¶1 for allegedly failing to "make any assurances that restrictions imposed on each of the [biological] deposits will be irrevocably removed upon granting of a patent" is respectfully traversed.

Applicants timely confirm that all unacceptable restrictions, including restriction on transfer of a deposit to a third party, will be so removed.

The Office Action further contends that from the deposit dates for each of the hybrodomas and the priority date for the Applicants' provisional application, "only claims for 14C7 hybridoma and antibody produced therefrom would receive benefit of the priority filing date." This is incorrect. The PTO's reliance on *Feldman* is misplaced. The PTO's position is contradictory to the case law holding that enablement is determined at the time of issuing of the patent, and these deposits made after filing are acceptable. See, *In re Lundak*, 227 U.S.P.Q. 90, 95 (Fed. Cir. 1985) and *In re Argoudelis*, 168 U.S.P.Q. 99 (CCPA 1970).

> "The enablement requirement of §112, first paragraph, does not require such assured access to a microorganism deposit *as of the filing date*; what is required is assurance of access (to the microorganism culture by the public upon issuance of a patent on the application) prior to *or during the pendency* of the application, so that, upon issuance of a U.S. patent on the application, "the public will, in fact, receive something in return for the patent grant." (Emphasis added)
>
> In re Argoudelis, 58 C.C.P.A. at 776, 434 F.2d at 1394 (Baldwin,J concurring)

See also 37 C.F.R. §1.804.

Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, second paragraph

Claims 61, 64, 65, 67–69 and 86–96 stand rejected under §112, ¶2 for allegedly failing to define the "metes and bounds" of the antibody molecules claimed in claim 61. Applicants respectfully disagree with this contention.

It is earnestly submitted that a skilled worker who is familiar with the techniques and/or reagents used in antibody engineering would possess a definitive understanding of what is described in Applicants' claims. Techniques for generating hybridomas, and use thereof, for example, in the production of immunologically reactive antibody molecules were well-appreciated before the filing date of the instant application. See, for example, Kohler et al., (Nature, vol. 7; pp. 495-497, 1975) as cited at page 49 of Applicants' instant specification. For example, the skilled worker could generate full-length antibody molecules having the immunospecificity and/or reactivity described in Applicants' specification, and use techniques of protein chemistry (for example, pepsin or trypsin digestion) to generate fragments of such molecules that are commensurate with the claims. Such methods are conventional; they are disclosed in Applicants' own specification and further described in the references cited therein. See, for example, the paragraphs bridging pages 55 and 56 of the instant specification, as originally filed. As such, both mature antibody molecules (i.e., containing all the distinct domains and/or regions of an antibody molecule) and fragments thereof can be derived from the same hybridoma using knowledge gathered from the disclosure contained in Applicants' own specification.

Alternatively, the skilled worker could rely on recombinant techniques, for example, art knowledge of cloning and/or phage display libraries to rapidly generate antibodies with slightly different structures and/or specificities compared to those derived from traditional approaches (for example, monoclonal antibodies). See, the enclosed WikiPedia reference article. Thus, the use of antibody fragments or even derivatives are clearly commensurate with the scope of the claims.

Applicants therefore submit that the claim language is sufficiently definite, especially in the context of Applicants' instant specification and the information available to the skilled worker prior to the filing of the instant application. Withdrawal of the rejection is respectfully requested.

Regarding claim 87, Applicants appreciate the Examiner's careful reading of the claims. The rejection, not specifically discussed herein, is moot in view of the amendments.

Rejection under 35 U.S.C. §112, first paragraph (written description)

Claims 48–56, 58–61 and 64, 65, 67–69 and 89–96 stand rejected under §112, ¶1 for allegedly failing to provide a written description of the claim term "derivatives." This rejection is respectfully traversed.

A skilled artisan, based on the disclosure contained in the specification and the art knowledge of antibodies, would recognize that the antibody derivative(s) having the disclosed structural elements (for example, amino acid sequence) and/or the functionality (for example, ability to bind to a class of polypeptides and/or epitopes thereof) could be routinely isolated and used in a manner described in Applicants' specification. Express description of such claim terms is not necessary. As described in the aforementioned paragraphs, a skilled artisan can routinely utilize recombinant techniques, for example, art knowledge of cloning and/or phage display libraries, to rapidly generate antibody derivatives with slightly different structures and/or specificities compared to the parent molecules (for example, monoclonal antibodies). However, in order to facilitate prosecution, claim 48 has been amended. Applicants' amendment of said claim is not to be construed as acquiescence to this or any other ground of rejection. The rejection is therefore moot in view of the amendments.

Rejection under 35 U.S.C. §112, first paragraph (enablement)

Claims 65, and 67–69 stand rejected under §112, ¶1 for allegedly failing to provide enablement of "pharmaceutical application in any method or for just any application, much less a treatment." This contention is respectfully traversed.

The Examiner finds the specification is enabling only for the pharmaceutical compositions but not for the uses disclosed. Applicants courteously request the examiner to clarify this contention. At the outset, Applicants submit that the instant claims are drawn to pharmaceutical composition(s) comprising the claimed antibody molecule(s). The recitation of the claim term "pharmaceutical" is not to be construed as limiting to the use thereof for example, in the treatment of diseases. For example,

diagnostic uses are possible. In the absence of evidence which demonstrate otherwise, all claims must be taken to satisfy the requirements of 35 U.S.C. §112, first paragraph. Moreover, only one use needs to be enabled for compound/composition claims. Here, the focus is on an anti-hepsin antibody molecule which is capable of binding to hepsin and is useful for the detection and targeting of tumor cells which express hepsin polypeptides. See, the disclosure contained in the Examples. See also the subject matter of claims 70–82, which are fully supported by the disclosure contained in Applicants' originally filed specification. The entirety of the Examiner's arguments concerning non-enablement is centered upon the assumption that the composition(s) are to be used medicinally. Insofar as the Office Action fails to address other enabling uses of the antibody molecules and compositions thereof, these allegations of non-enablement is respectfully traversed. Furthermore, Applicants urge the Patent Office to examine the full scope of the claims in light of what is disclosed in the specification.

Applicants maintain all pending claims clearly satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. The Office Action relies on the *Wands* factors and allegations that the claims are very broad with respect to the use of the pharmaceutical composition, for example, in the treatment of diseases. Applicants respectfully disagree with this allegation.

The instant specification describes a role of hepsin polypeptide in the etiology of cancer. For example, see, the paragraphs bridging page 1 and 2 of the instant specification, as originally filed. It is described therein that hepsin is a serine protease which is expressed in deregulated amounts in cancer cells. See, page 4, 2nd paragraph. Mechanisms via which hepsin may play a role in imparting cancerous phenotype is described in, for example, the paragraph bridging pages 5 and 6 of the instant specification. The rationale for the use of targeted delivery of agents and/or compositions against hepsin, which in turn provides effective means for targeting malignant cells that over-express hepsin polypeptides or its fragments is clearly provided in the instant specification. See, for example page 6, lines 4–10. The activity of antibody molecules against tumors is also clearly described. Using various biochemical and immunological assays, the specification provides an enabling disclosure of the *in vitro* and *in vivo* activity of claimed antibody molecules. A skilled artisan, in view of the detailed disclosure contained in the specification and the art knowledge of pharmacology would readily appreciate that the claimed molecules and/or

compositions can be used in a manner described in Applicants' claims. Nothing more than routine experimentation would be required.

Furthermore, the use of antibody molecules in the detection and/or destruction of cancer cells is a phenomena that is well-recognized in the art. For example, antibody molecules directed against growth factor receptors and the like represent viable alternatives to the use of small molecules in the treatment and even prevention of a host range of diseases. In this regard, Applicants' specification provides a detailed description of the use of anti-hepsin antibody molecules in the detection and/or targeted therapy of neoplastic diseases. For example, see, the disclosure contained in the paragraphs bridging line 5, page 53 to line 5, page 54 of the instant specification, as originally filed. The specification discloses enabling uses of antibody molecules, not only for detection of hepsin, but also for neutralization of hepsin molecules and/or activity thereof. For example, Fig. 15 (panels A to D), discloses that monoclonal antibodies (for example, mAb species 11C1, 47A5, 38E2, 46D12, 37G10, 14C7, 31C1, 72H6 or 14C7) bind to hepsin with immunospecificity. Fig. 16A outlines a use of polyclonal antibodies against hepsin polypeptides in the detection of human prostate tumor. Panels B and C of Fig. 16 describe the use of anti-hepsin hybridomas and monoclonal antibodies resulting therefrom for the detection of human prostate tumor tissue. The study is based using a mouse hybridoma which generates anti-hepsin mAb11C1 (panel B) or the corresponding monoclonal antibody species 11C1.

In summary, the specification provides enabling disclosures pertaining to the use of polyclonal antibodies, monoclonal antibodies, and/or hybridomas in the detection of tumor cells. Applicants' specification also provides an enabling disclosure for the use of such antibody species in therapeutics. For example, in Fig. 19, the neutralization of hepsin activity by a purified monoclonal antibody is discribed in detail. Based on the disclosure contained in the specification regarding perturbed activity of hepsin molecules in the tumor progression, a skilled artisan can appreciate that the neutralizing effect of the claimed antibodies could be utilized in pharmaceutical applications. This would constitute nothing more than routine experimentation.

In contrast, the present Office Action has not presented any evidence to refute the findings described in Applicants' specification; nor has the Office Action established any scientific credibility to support the contention that the claimed compositions could not be prepared and/or used in a manner described herein. Therefore, the rejection

under 35 U.S.C. §112 is completely unfounded.

Given the extent of the disclosure provided, it would have at most involved routine experimentation, if any at all, for one skilled in the art to use the claimed molecules as pharmaceutical compositions. For example, see, page 7, lines 25–30. Formulations which confer targeted delivery or desired efficacy are routinely known in the art. Even absent the disclosure as discussed above, the rejection is clearly deficient under general controlling case law. The courts have placed a burden on the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated. See example *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to make and use the compositions recited in the claims. Instead of evidence of non-enablement, the Examiner cites the lack of predictability in the field of the cancer in requiring additional working examples. The Examiner is requiring that the applicant meet the clinical standards as set forth by the FDA to satisfy that enablement requirement under 35 U.S.C. §112, first paragraph. This is clearly not the intention of the statute. See, *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969). A lack of predictability can be addressed by routine experimentation which is permissible under the statute. A considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to direction which the experimentation should proceed (see *In re Wands* cited by the Examiner). Moreover, as stated in *In re Brana*, 51 F.3d 1516, 34 USPQ 1436 (Fed. Cir. 1995), an Applicant is not required to test the claimed compounds in their final use. The same rationale applies to meeting the enablement and disclosure requirements of 35 U.S.C. §112, first paragraph. The specification provides more than it needs, for example, *in vitro* assays and *in vivo* assays. In similar fashion, one of ordinary skill in the art by performing the same or similar tests can by routine experimentation determine the activity levels of each of the claimed compounds in treating various cancers.

For the reasons discussed above, applicants submit all pending claims satisfy the requirements of 35 U.S.C. §112, first paragraph. Withdrawal of the rejection is respectfully requested.

Rejoinder

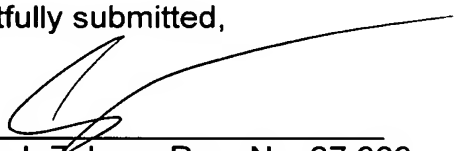
Previously withdrawn method of use claims (claims 70–82) recite all the features of Applicants' antibody molecule(s) of claim 48. "If a product claim is found allowable, process claims that depend from or otherwise require all the limitations of the patentable product may be rejoined." See M.P.E.P. § 821.04 (b).

The withdrawn method, which fully comply with the statutory requirements under §101 and §112, are being retained in the application. Applicants respectfully request rejoinder thereof in accordance with the practice in In re Ochiai, 37 USPQ2d 1127 (Fed. Cir. 1995) and In re Brouwer, 37 USPQ2d 1663 (Fed. Cir. 1996). See, also the Commissioner's notice in 1184 TMOG 86, March 26, 1996.

In view of the above remarks, it is courteously submitted that the application is in condition for allowance. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,



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Monoclonal antibodies

From Wikipedia, the free encyclopedia
(Redirected from Monoclonal antibody)

Mŏnoclonal antibodies (**mAb** or **moAb**) are antibodies that are identical because they were produced by one type of immune cell and are all clones of a single parent cell. Given (almost) any substance, it is possible to create monoclonal antibodies that specifically bind to that substance; they can then serve to detect or purify that substance. This has become an important tool in biochemistry, molecular biology and medicine. When used as medications, the generic name ends in *-mab* (see "Nomenclature of monoclonal antibodies").

Contents

Discovery

The idea of a "magic bullet" was first proposed by Paul Ehrlich who at the beginning of the 20th century postulated that if a compound could be made that selectively targeted a disease-causing organism, then a toxin for that organism could be delivered along with the agent of selectivity.

In the 1970s the B-cell cancer myeloma was known, and it was understood that these cancerous B-cells all produce a single type of antibody (a paraprotein). This was used to study the structure of antibodies, but it was not yet possible to produce identical antibodies specific to a given antigen.

The process of producing monoclonal antibodies described above was invented by Georges Köhler, César Milstein, and Niels Kaj Jerne in 1975;[1] they shared the Nobel Prize in Physiology or Medicine in 1984 for the discovery. The key idea was to use a line of myeloma cells that had lost their ability to secrete antibodies, come up with a technique to fuse these cells with healthy antibody producing B-cells, and be able to select for the successfully fused cells.

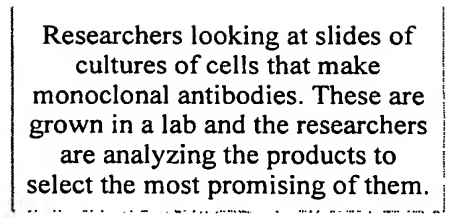
In 1988 Greg Winter and his team pioneered the techniques to humanise monoclonal antibodies,[2] removing the reactions that many monoclonal antibodies caused in some patients.

Production

Hybridoma

Monoclonal antibodies can be produced in cell culture or in live animals. If a foreign substance (an antigen) is injected into a vertebrate such as a mouse or a human, some of the immune system's B-cells will turn into plasma cells and start to produce antibodies that recognize that antigen. Each B-cell produces only one kind of antibody, but different B-cells will produce structurally different antibodies that bind to different parts ("epitopes") of the antigen. This natural mixture of antibodies found in

serum is known as polyclonal antibodies.



Researchers looking at slides of cultures of cells that make monoclonal antibodies. These are grown in a lab and the researchers are analyzing the products to select the most promising of them.

To produce *monoclonal* antibodies, the B-cells from the spleen or lymph nodes are removed from an animal that has been challenged several times with the antigen of interest. These B-cells are then fused with myeloma tumor cells that can grow indefinitely in culture (myeloma is a B-cell cancer or more specifically a plasmacytoma) and that have lost the ability to produce antibodies. This fusion is done by making the cell membranes more permeable by the use of polyethylene glycol (PEG), electroporation or, of historical importance, infection with some virus. The fused hybrid cells (called hybridomas), being cancer cells, will multiply rapidly and indefinitely. Large amounts of antibodies can therefore be produced. The hybridomas are sufficiently diluted to ensure clonality (all cells in the culture stem from the same single cell) and grown. The antibodies from the different clones are then tested for their ability to bind to the antigen (for example with a test such as ELISA or Antigen Microarray Assay) or immuno-dot blot, and the most sensitive one is picked out. When the hybridoma cells are injected in mice (in the peritoneal cavity, the gut), they produce tumors containing an antibody-rich fluid called ascites fluid.

In the above process, myeloma cell lines that have lost their ability to produce their own antibodies or antibody chain are used, so as to not contaminate the target antibody. Furthermore, only myeloma cells that have lost a specific enzyme called hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and therefore cannot grow under certain conditions (e.g. in the presence of a selection medium called HAT medium) are used; these cells are preselected by the use of either 8-azaguanine or 6-thioguanine(8-azaguanine has been shown to produce unreliable results.(van Diggelen et al 1979)) media prior to the fusion since cells that possess the HGPRT will be killed by the 8-azaguanine. During the fusion process many cells can fuse: Myeloma cell with myeloma cell, spleen cell with spleen cell, spleen cell with myeloma cell, etc. The desired fusions for making hybridomas are between a healthy B-cell, which produces antibodies against the antigen of interest, and a myeloma cell. In these relatively rare fusions, the healthy B cell will make the HGPRT enzyme that will allow the fused cell to survive in HAT medium so that only the successfully fused cells will grow in culture. The medium must be enriched during selection to favour hybridoma growth. This can be achieved by the use of a layer of feeder cells or supplement media such as briclone. Production in cell culture is usually preferred as the ascites technique may be very painful to the animal and if replacement techniques exist, may be considered unethical.

Recombinant

The production of Recombinant monoclonal antibodies involves technologies, referred to as *repertoire cloning* or *phage display/yeast display*. Recombinant antibody engineering involves the use of viruses or yeast to create antibodies, rather than mice. These techniques rely on rapid cloning of immunoglobulin gene segments to create libraries of antibodies with slightly different amino acid sequences from which antibodies with desired specificities can be selected.[3] These techniques can be used to enhance: the specificity with which antibodies recognize antigens, their stability in various environmental conditions, their therapeutic efficacy, and their detectability in diagnostic applications.[4] Fermentation chambers have been used to produce these antibodies on a large scale.

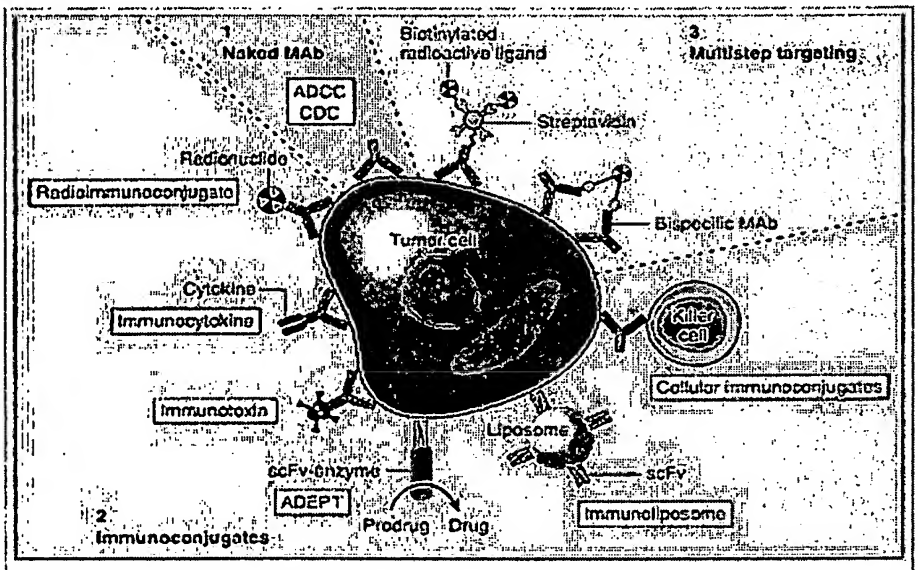
Applications

Once monoclonal antibodies for a given substance have been produced, they can be used to detect the presence and quantity of this substance, for instance in a Western blot test (to detect a protein on a membrane) or an immunofluorescence test (to detect a substance in a cell). They are also very useful in immunohistochemistry which detect antigen in fixed tissue sections. Monoclonal antibodies can also be used to purify a substance with techniques called immunoprecipitation and affinity chromatography.

Monoclonal antibodies for cancer treatment

One possible treatment for cancer involves monoclonal antibodies that bind only to cancer cell-specific

antigens and induce an immunological response against the target cancer cell. Such mAb could also be modified for delivery of a toxin, radioisotope, cytokine or other active conjugate; it is also possible to design bispecific antibodies that can bind with their Fab regions both to target antigen and to a conjugate or effector cell. In fact, every intact antibody can bind to cell receptors or other proteins with its Fc region. The illustration below shows all these possibilities:



Monoclonal antibodies for cancer. ADEPT, antibody directed enzyme prodrug therapy; ADCC, antibody dependent cell-mediated cytotoxicity; CDC, complement dependent cytotoxicity; MAb, monoclonal antibody; scFv, single-chain Fv fragment.[5]

Chimeric and humanized antibodies

One problem in medical applications is that the standard procedure of producing monoclonal antibodies yields mouse antibodies. Although murine antibodies are very similar to human ones there are differences. The human immune system hence recognizes mouse antibodies as foreign, rapidly removing them from circulation and causing systemic inflammatory effects.

A solution to this problem would be to generate human antibodies directly from humans. However, this is not easy, primarily because it is generally not seen as ethical to challenge humans with antigen in order to produce antibody; while the ethics of doing the same to non-humans is a matter of debate. Furthermore, it is not easy to generate human antibodies against human tissues.

Various approaches using recombinant DNA technology to overcome this problem have been tried since the late 1980s. In one approach, one takes the DNA that encodes the binding portion of monoclonal mouse antibodies and merges it with human antibody producing DNA. One then uses mammalian cell cultures to express this DNA and produce these half-mouse and half-human antibodies. (Bacteria cannot be used for this purpose, since they cannot produce this kind of glycoprotein.) Depending on how big a part of the mouse antibody is used, one talks about **chimeric antibodies** or **humanized antibodies**. Another approach involves mice genetically engineered to produce more human-like antibodies. Monoclonal antibodies have been generated and approved to treat: cancer, cardiovascular disease, inflammatory diseases, macular degeneration, transplant rejection, multiple sclerosis, and viral infection (see monoclonal antibody therapy).

In August 2006 the Pharmaceutical Research and Manufacturers of America reported that U.S. companies had 160 different monoclonal antibodies in clinical trials or awaiting approval by the Food and Drug Administration.[6]

See also

- Monoclonal antibody therapy
- Nomenclature of monoclonal antibodies
- Polyclonal antibody
- Nanobodies

References

1. ^ Kohler G, Milstein C. *Continuous cultures of fused cells secreting antibody of predefined specificity.* Nature 1975;256:495-7. PMID 1172191. Reproduced in J Immunol 2005;174:2453-5. PMID 15728446.
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4. ^ Schmitz U, Versmold A, Kaufmann P, Frank HG (2000). "Phage display: a molecular tool for the generation of antibodies--a review". *Placenta* **21 Suppl A**: S106-12. PMID 10831134.
5. ^ Modified from Carter P: Improving the efficacy of antibody-based cancer therapies. Nat Rev Cancer 2001;1:118-129
6. ^ *PhRMA Reports Identifies More than 400 Biotech Drugs in Development.* Pharmaceutical Technology, August 24, 2006. Retrieved 2006-09-04.

External links

- Monoclonal Antibodies, from John W. Kimball's online biology textbook
- MeSH *Monoclonal+antibodies*

Monoclonal antibodies
Rat-murine hybrid monoclonal antibodies [hide]
Catumaxomab, Ertumaxomab

Categories: Immunology | Biotechnology | Immune system | Monoclonal antibodies